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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/757,803	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/13/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

JDO

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 7/20/2005 has been considered. Each of the rejections of record is considered moot with regards to the rejected claims since each of the rejected claims have been cancelled. Rejections and/or objections not reiterated from the previous office action mailed 5/31/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-17 have been cancelled. Claims 18-38 are pending in the application.

New Objections/Rejections

Claim Objections

Claim 24 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 23. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, claims 23 and 24 are identical.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are phrased, for example, to read on "the siNA molecule of 18". It appears as if applicant intends for the claims to be drawn to, for example, "the siNA molecule of **claim** 18". Insertion of the word "claim" into each of claims 19-38 would obviate this rejection. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In the instant case, the effective filing date is determined to be that of the parent application of PCT/US03/05346, which has an effective filing date of 2/20/03. The instant claims of application 10/757,803 do not receive the benefit of PCT/US03/05028 or earlier, or of 10/427,160 or PCT/US02/15876, because these documents do not disclose siNA molecules with a limitation of 19 to 29 nucleotides in length. Thus, the instant claims are accorded an effective filing date of 2/20/03.

Claims 18-22, 25, 27, and 29-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Matulic-Adamic et al. (U.S. 5,998,203).

The invention of the above claims is drawn to a double stranded short interfering nucleic acid (siNA) molecule that comprises a first and a second strand, the first strand comprises a sense region and the second strand comprises an antisense region, each strand is 19 to 29 nucleotides in length, and the first strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both the 5' and 3' ends. The cap moiety comprises an abasic moiety, more specifically an inverted deoxyabasic moiety, an inverted nucleotide moiety, or a non-nucleotide moiety. The siNA is assembled from two

separate fragments wherein one fragment comprises the sense region and a second fragment comprises the antisense region. The sense region is connected to the antisense region via a polynucleotide or non-nucleotide linker. The invention is further drawn to modified nucleotides and a pharmaceutical composition comprising the siNA and an acceptable carrier or diluent.

The term "siNA" is defined in the instant specification, page 76, as referring to any nucleic acid molecule capable of inhibiting or down regulating gene expression or viral replication, for example by mediating RNA interference or gene silencing in a sequence-specific manner. Matulic-Adamic et al. teach double stranded short interfering nucleic acid molecules that comprise a first nucleotide sequence complementary to a target or a portion thereof, and a second sequence having complementarity to said first sequence. Matulic-Adamic et al. teach chemical modifications of the double stranded structure. The ribozymes taught by Matulic-Adamic et al. comprise ribonucleotides and cleave other separate RNA molecules in a nucleotide base sequence-specific manner. Such enzymatic RNA molecules are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. For example, figure 3 contains a ribozyme structure that meets the structural limitations of the instant claims (see figure 3 and description of figure 3 in column 7). When 100% of the nucleotide positions are modified, the duplex is considered to comprise no ribonucleotides. The modifications can be in one or both of the strands. Helix 4 can be formed from two separate molecules, i.e. without a connecting loop. Further, the

connecting loop (nucleotide linker) can also be replaced with a non-nucleotide linker (see column 8). When the connecting loop ($(N)_q$) is not present, the ribozyme is formed from two separate strands. Applicant argues that the genus of ribozymes taught by Matulic-Adamic et al. have various sizes and structures depending on values of m, n, o, p, q and s. On the contrary, when the connecting loop is not present, each strand is 19 to 29 nucleotides in length without any modification to the values of m, n, o, p, q and s. The first strand comprises a sense region that has complementarity to an antisense region (see helix 3 or helix 4). The second strand comprises an antisense region that is complementary to the target (see the portion of the second strand that is complementary to the substrate RNA). As defined in the instant specification, page 82, "by antisense region is meant a nucleotide sequence of a siNA molecule having complementarity to a target nucleic acid sequence. In addition, the antisense region of a siNA molecule can **optionally** comprise a nucleic acid sequence having complementarity to a sense region of the siNA molecule". The ribozyme taught by Matulic-Adamic et al. meets the instant definition of having a sense and an antisense region, as well as the instant definition of a siNA, as evidenced by the fact that they hybridize with each other. Further, i*n vitro* RNA cleavage was carried out in reaction buffers containing water, which is a pharmaceutically acceptable diluent. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al.

teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). Applicant has argued that the molecules taught by Matulic-Adamic et al. have 4 or more nucleotide long internal loop structures that are not required for the instantly claimed siNA molecules. This argument is not convincing. It is well established in the case law that the prior art can teach additional elements provided that the prior art teaches the instantly claimed elements. Therefore, the ribozyme taught by Matulic-Adamic et al. meets each of the structural limitations of instant claims 18-22, 25, 27, and 29-38.

Claims 18-22, 25, 28, 29, 33, 34, 37 and 38 are rejected under 35 U.S.C. 102 (b) as being anticipated by Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001).

The invention of the above claims is drawn to a double stranded short interfering nucleic acid (siNA) molecule that comprises a first and a second strand, the first strand comprises a sense region and the second strand comprises an antisense region, each strand is 19 to 29 nucleotides in length, and the first strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both the 5' and 3' ends. The cap moiety comprises an abasic moiety, more specifically an inverted deoxyabasic moiety, or an inverted nucleotide moiety. The siNA is assembled from two separate fragments wherein one

fragment comprises the sense region and a second fragment comprises the antisense region. The invention is further drawn to modified nucleotides and a pharmaceutical composition comprising the siNA and an acceptable carrier or diluent.

Elbashir et al. teach chemically synthesized siRNA duplexes consisting of two separate RNA strands, wherein each strand is 21-23 nucleotides in length, preferably 21 nucleotides. The siRNA duplexes taught by Elbashir et al. comprise a sense and an antisense strand (see figure 1, for example). Elbashir et al. teach 2'- deoxy or 2'-O-methyl modification of the 3' overhanging nucleotides, meeting the instant limitation of a terminal cap moiety. Applicant argues that Elbashir et al. cannot anticipate the present claims because Elbashir et al. do not teach terminal caps. On the contrary, applicant has not defined "terminal cap" and it is not a term of the art, but has disclosed examples in figure 22 including deoxyribonucleotides. Therefore, this terminology is interpreted broadly to include any nucleotide. Additionally, Elbashir et al. teach siRNA duplexes that are 100% modified, which are considered to comprise no ribonucleotides. For example, Elbashir et al. teach complete substitution of one or both siRNA strands by 2' deoxy residues or 2'-O-methyl residues. Elbashir et al. teach 2'-deoxythymidine and 2'-deoxy-guanosines (see figure 7). The reactions taught by Elbashir et al. were carried out in buffers, which are considered pharmaceutically acceptable. Therefore, the instant invention is anticipated by Elbashir et al.

Claims 18, 20, 21, 28, 29, 35, 36 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000).

The invention of the above claims is drawn to a double stranded short interfering nucleic acid (siNA) molecule that comprises a first and a second strand, the first strand comprises a sense region and the second strand comprises an antisense region, each strand is 19 to 29 nucleotides in length, and the first strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both the 5' and 3' ends. The cap moiety comprises an abasic moiety. The siNA is assembled from two separate fragments wherein one fragment comprises the sense region and a second fragment comprises the antisense region. The invention is further drawn to modified nucleotides and a pharmaceutical composition comprising the siNA and an acceptable carrier or diluent.

Parrish et al. teach chemically synthesized double stranded siNA molecules comprising a first nucleotide sequence with complementarity to a target and a second nucleotide sequence with complementarity to said first nucleotide sequence, wherein said second nucleotide sequence is modified and at least 19 nucleotides are complementary between the first and second sequences. The siRNA duplexes taught by Parrish et al. comprise a sense and an antisense strand. Each of the strands of the siRNA duplexes taught by Parrish et al. comprise 26 nucleotides. Parrish et al. teach siNA molecules comprising ribonucleotides. Parrish et al. teach that certain modifications were well tolerated on the sense, but not the antisense strand, indicating that the two trigger strands have distinct roles in the interference process (see summary). Parrish et al. teach 2'-deoxy-2'-fluoro pyrimidine modifications in the sense or antisense strand (see figure 5). Applicant argues that Parrish et al. cannot anticipate the present claims because Parrish et al. do not teach terminal caps. On the contrary,

applicant has not defined "terminal cap" and it is not a term of the art, but has disclosed examples in figure 22 including deoxyribonucleotides. Therefore, this terminology is interpreted broadly to include any nucleotide. The modifications taught by Parrish et al. meet the instant limitation of comprising a terminal cap moiety. The assays taught by Parrish et al. comprise buffers (i.e. water) that are considered a pharmaceutically acceptable diluent. Therefore, the instant invention is anticipated by Parrish et al.

Claims 18-22 and 25-38 are rejected under 35 U.S.C. 102(e) as being anticipated by McSwiggen (US 2004/0019001 A1).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The invention of the above claims is drawn to a double stranded short interfering nucleic acid (siNA) molecule that comprises a first and a second strand, the first strand comprises a sense region and the second strand comprises an antisense region, each strand is 19 to 29 nucleotides in length, and the first strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both the 5' and 3' ends. The cap moiety comprises an abasic moiety, more specifically an inverted deoxyabasic moiety, an inverted nucleotide moiety, a non-nucleotide moiety, or a LNA moiety. The siNA is assembled

from two separate fragments wherein one fragment comprises the sense region and a second fragment comprises the antisense region. The sense region is connected to the antisense region via a polynucleotide or non-nucleotide linker. The invention is further drawn to modified nucleotides and a pharmaceutical composition comprising the siNA and an acceptable carrier or diluent.

McSwiggen teaches chemically synthesized double stranded siRNA molecules wherein the siRNA comprises a first and a second strand, the first strand comprises a sense region and the second strand comprises an antisense region, each strand is about 19 to about 25 nucleotides, and the first strand comprises a terminal cap molecule at the 3', 5', or both 3' and 5'-ends (see page 7 for example). McSwiggen teaches siRNA duplexes wherein each strand comprises 19 nucleotides that are complementary to the other strand. McSwiggen teaches inverted deoxyabasic residue incorporation (see page 5) and inverted nucleotides (see page 7). McSwiggen teaches the incorporation of LNA nucleotides (see page 9). McSwiggen teaches that the siRNA can be assembled from two separate fragments wherein one fragment comprises the sense region and one fragment comprises the antisense region (see page 3). The sense region and the antisense region can be covalently connected via a linker molecule, wherein the linker molecule can be a polynucleotide or a non-nucleotide linker. McSwiggen teaches each of the instantly claimed modifications and types of nucleotides. The pyrimidine nucleotides in the sense region can be 2'-O-methyl modified and the pyrimidine nucleotides in the antisense region can by 2'-deoxy-2'-fluoro modified. McSwiggen teaches compositions comprising the siRNA and an

acceptable carrier or diluent. Therefore, the instant invention is anticipated by McSwiggen.

Claims 18, 20-22, 25, 27-29 and 33-38 are rejected under 35 U.S.C. 102 (a) or (e) as being anticipated by Tuschl et al. (WO 02/44321 A2).

The invention of the above claims is drawn to a double stranded short interfering nucleic acid (siNA) molecule that comprises a first and a second strand, the first strand comprises a sense region and the second strand comprises an antisense region, each strand is 19 to 29 nucleotides in length, and the first strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both the 5' and 3' ends. The cap moiety comprises an abasic moiety, more specifically an inverted deoxyabasic moiety, an inverted nucleotide moiety, or a non-nucleotide moiety. The siNA is assembled from two separate fragments wherein one fragment comprises the sense region and a second fragment comprises the antisense region. The invention is further drawn to modified nucleotides and a pharmaceutical composition comprising the siNA and an acceptable carrier or diluent.

Tuschl et al. teach chemically synthesized siRNA duplexes consisting of two separate RNA strands, wherein each strand is 19-25 nucleotides, preferably 21 nucleotides (see pages 3 and 7). One strand of the duplex is preferably 100% complementary to the target (see page 6). Tuschl et al. disclose that the dsRNA of their invention can be 21 nucleotide siRNA duplexes with 3' overhangs or with blunt ends wherein the two strands are fully complementary to each other and one strand is

fully complementary to at least part of a transcript of a target gene (see page 44, line 25, and figure 11). The most effective dsRNAs are composed of two 21 nt strands which are paired such that 1-3, preferably 2 nt 3' overhangs are present on both ends of the dsRNA. Tuschl et al. teach chemical modifications at the 5' and/or the 3' end of the dsRNA molecule (see page 5) for stabilization against degradation. Tuschl et al. teach the incorporation of nucleotide analogues at the 5' and/or 3' end for stabilization. Tuschl et al. teach replacement of the 2' OH group by a group including H or a halo, where the halo is F, Cl, Br or I. These modifications meet the limitations of the instantly claimed "terminal cap moieties". Applicant has not defined "terminal cap", but has disclosed examples in figure 22 including deoxyribonucleotides. Tuschl et al. teach replacement of uridine residues with 2'-deoxy thymidine at the 3' ends, which is an abasic moiety. Tuschl et al. teach 2'-deoxy, 2'-O sugar modifications and phosphorothioates. Tuschl et al. teach pharmaceutical compositions comprising the siRNA and a carrier or diluent. Tuschl et al. teach that siRNAs represent a new alternative to antisense or ribozyme therapeutics. Therefore, the instant invention is anticipated by Tuschl et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), in view of Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), Cook et al. (US 5,587,471), Wengel et al. (WO 99/14226), and Morrissey et al. (US 2003/0206887 A1).

The invention of the above claims is drawn to a double stranded short interfering nucleic acid (siNA) molecule that comprises a first and a second strand, the first strand comprises a sense region and the second strand comprises an antisense region, each strand is 19 to 29 nucleotides in length, and the first strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both the 5' and 3' ends. The cap moiety comprises an abasic moiety, more specifically an inverted deoxyabasic moiety, an inverted nucleotide moiety, a non-nucleotide moiety, a LNA moiety, or a glyceryl moiety. The siNA is assembled from two separate fragments wherein one fragment comprises the sense region and a second fragment comprises the antisense region. The sense region is connected to the antisense region via a polynucleotide or non-nucleotide linker. The invention is further drawn to modified nucleotides and a pharmaceutical composition comprising the siNA and an acceptable carrier or diluent.

Elbashir et al. teach chemically synthesized siRNA duplexes consisting of two separate RNA strands, wherein each strand is 21-23 nucleotides in length, preferably 21 nucleotides. The siRNA duplexes taught by Elbashir et al. comprise a sense and an antisense strand (see figure 1, for example). Elbashir et al. teach 2'- deoxy or 2'-O-methyl modification of the 3' overhanging nucleotides, meeting the instant limitation of a terminal cap moiety. Applicant argues that Elbashir et al. cannot anticipate the present

claims because Elbashir et al. do not teach terminal caps. On the contrary, applicant has not defined "terminal cap" and it is not a term of the art, but has disclosed examples in figure 22 including deoxyribonucleotides. Therefore, this terminology is interpreted broadly to include any nucleotide. Additionally, Elbashir et al. teach siRNA duplexes that are 100% modified, which are considered to comprise no ribonucleotides. For example, Elbashir et al. teach complete substitution of one or both siRNA strands by 2' deoxy residues or 2'-O-methyl residues. Elbashir et al. teach 2'-deoxythymidine and 2'-deoxy-guanosines (see figure 7). The reactions taught by Elbashir et al. were carried out in buffers, which are considered pharmaceutically acceptable.

Elbashir et al. do not teach glyceryl moieties, LNA moieties, polynucleotide or non-nucleotide linkers, or 2'-deoxy-2'fluoro pyrimidine nucleotides.

Parrish et al. teach chemically synthesized double stranded siRNA molecules comprising a first nucleotide sequence with complementarity to a target and a second nucleotide sequence with complementarity to said first nucleotide sequence, wherein one or both of the nucleotide sequences are modified and at least 19 nucleotides are complementary between the first and second sequences. The siRNA molecules are an antisense/sense pair of oligomers. The siRNA molecules taught by Parrish et al. comprise 26 nucleotides. Parrish et al. teach siRNA molecules comprising ribonucleotides. Parrish et al. teach 2'-deoxy-2'-fluoro pyrimidine modifications in the sense or antisense strand, as well as (see figure 5). The assays taught by Parrish et al. comprise buffers (i.e. water) that are considered a pharmaceutically acceptable diluent.

Cook et al. teach various conjugates and modifications that can be incorporated into oligonucleotides to improve the pharmacokinetic properties of an oligonucleotide, including glyceryl (see columns 2 and 3).

Wengel et al. teach that LNAs are able to provide valuable improvements to oligonucleotides with respect to affinity and specificity towards complementary RNA and DNA. Wengel et al. teach that LNAs are useful in a wide range of applications, including antisense applications (see abstract).

Morrissey et al. teach siNA duplexes wherein the sense strand and the antisense strand are covalently connected via a linker, wherein the linker can be a polynucleotide or non-nucleotide linker. Morrissey et al. teach that siNA molecules can be synthesized as a single continuous oligonucleotide separated by a cleavable polynucleotide or non-nucleotide linker which is subsequently cleaved to provide separate siNA fragments or strands (see page 24).

It would have been obvious to one of ordinary skill in the art to incorporate glyceryl moieties, LNA moieties, polynucleotide or non-nucleotide linkers, or 2'-deoxy-2'fluoro pyrimidine nucleotides, as taught by Cook et al., Wengel et al., Morrissey et al., and Parrish et al., respectively, into the siRNA molecules taught by Elbashir et al.

One would have been motivated to create such compounds because Cook et al. teach that glyceryl can be used to improve the pharmacokinetics of oligonucleotides, Wengel et al. teach that LNAs provide valuable improvements to oligonucleotides with respect to affinity and specificity towards complementary RNA, and Parrish et al. teach the application of 2'-deoxy-2'-fluoro pyrimidine modifications in the sense or antisense

strand or an siRNA duplex. Additionally, Morrissey et al. teach the synthesis of siNA molecules as a single continuous oligonucleotide separated by a cleavable polynucleotide or non-nucleotide linker which is subsequently cleaved to provide separate siNA fragments or strands. Since Elbashir et al. teaches siRNA duplexes that have been modified and act via RNAi, and further teach testing modifications for their effect on RNAi, one would have been motivated to incorporate glyceryl moieties, LNA moieties, or 2'-deoxy-2'fluoro pyrimidine nucleotides, as taught by Cook et al., Wengel et al., and Parrish et al., respectively, since each of these modifications were known in the art at the time the invention was made to add benefits to oligonucleotides. Further, one would have been motivated to utilize polynucleotide or non-nucleotide linkers as taught by Morrissey et al. because Morrissey teaches that this is a method of synthesizing siNA molecules.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to oligonucleotides. One would expect for such modifications to benefit siRNA duplexes, as each had shown to benefit other oligonucleotides such as antisense oligonucleotides. One would reasonably expect for polynucleotide or non-nucleotide linkers as taught by Morrissey et al. to benefit the instant invention since such linkers were known in the art to aid in the production of siNA molecules.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 18-24 and 28-38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9-19, 22 and 31 of copending Application No. 10/877,889. Although the conflicting claims are not identical, they are not patentably distinct from each other because the species recited in the claims of application 10/877,889 anticipate the instant genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The invention of the above claims is drawn to a double stranded short interfering nucleic acid (siNA) molecule that comprises a first and a second strand, the first strand comprises a sense region and the second strand comprises an antisense region, each strand is 19 to 29 nucleotides in length, and the first strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both the 5' and 3' ends. The cap moiety comprises a

glyceryl moiety. The siNA is assembled from two separate fragments wherein one fragment comprises the sense region and a second fragment comprises the antisense region. The sense region is connected to the antisense region via a polynucleotide or non-nucleotide linker. The invention is further drawn to modified nucleotides and a pharmaceutical composition comprising the siNA and an acceptable carrier or diluent.

Application '889 recites a chemically synthesized double stranded siNA molecule that directs cleavage of an amyloid precursor protein (APP) RNA via RNA interference wherein each strand is about 18 to about 23 nucleotides in length and one strand comprises nucleotide sequence having sufficient complementarity to said APP RNA. The siNA molecules of application '889 are about 18 to about 23 nucleotides in length, which is interpreted as encompassing 19 to 29, as instantly claimed. The siNA molecules of application '889 comprise a sense and antisense region, wherein the molecule is assembled from two separate fragments. The sense region is connected to the antisense region via a polynucleotide or non-nucleotide linker. Claims 13-15, 18 and 19 of application '889 recite the same modifications as recited in instant claims 33-37. Further, application '889 recites the inclusion of a terminal cap moiety at the 5'-end, 3'-end, or both, more specifically an inverted deoxy abasic moiety, as well as a glyceryl modification. Although the siNA molecules of application '889 are specifically targeted to APP RNA, the siNA molecules meet each structural limitation of the instant claims and would therefore anticipate the broader genus of instantly claimed siNA molecules that are not targeted to any specific gene.

Claims 18-24 and 28-38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9-19, 22 and 31 of copending Application No. 10/918,987. Although the conflicting claims are not identical, they are not patentably distinct from each other because the species recited in the claims of application 10/918,987 anticipate the instant genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The invention of the above claims is drawn to a double stranded short interfering nucleic acid (siNA) molecule that comprises a first and a second strand, the first strand comprises a sense region and the second strand comprises an antisense region, each strand is 19 to 29 nucleotides in length, and the first strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both the 5' and 3' ends. The cap moiety comprises a glyceryl moiety. The siNA is assembled from two separate fragments wherein one fragment comprises the sense region and a second fragment comprises the antisense region. The sense region is connected to the antisense region via a polynucleotide or non-nucleotide linker. The invention is further drawn to modified nucleotides and a pharmaceutical composition comprising the siNA and an acceptable carrier or diluent.

Application '987 recites a chemically synthesized double stranded siNA molecule that directs cleavage of a VCAM-1 RNA via RNA interference wherein each strand is about 18 to about 23 nucleotides in length and one strand comprises nucleotide sequence having sufficient complementarity to said VCAM-1 RNA. The siNA molecules of application '987 are about 18 to about 23 nucleotides in length, which is interpreted

as encompassing 19 to 29, as instantly claimed. The siNA molecules of application '987 comprise a sense and antisense region, wherein the molecule is assembled from two separate fragments. The sense region is connected to the antisense region via a polynucleotide or non-nucleotide linker. Claims 13-15, 18 and 19 of application '987 recite the same modifications as recited in instant claims 33-37. Further, application '987 recites the inclusion of a terminal cap moiety at the 5'-end, 3'-end, or both, more specifically an inverted deoxy abasic moiety, as well as a glyceryl modification. Although the siNA molecules of application '987 are specifically targeted to VCAM-1 RNA, the siNA molecules meet each structural limitation of the instant claims and would therefore anticipate the broader genus of instantly claimed siNA molecules that are not targeted to any specific gene.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Amy H. Bowman
Examiner
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